PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 20990PC INS 2	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/004132	International filing date *(day/month/year)* 02.04.2004	Priority date *(day/month/year)* 02.04.2003
International Patent Classification (IPC) or national classification and IPC C07K14/47, C07K14/72		
Applicant INSTITUT NATIONAL DE LA SANTE ET DE LA RE... et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.09.2004	14.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Mabit, H Telephone No. +49 89 2399-7270

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/004132

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-17	as originally filed
Sequence listings part of the description, Pages	
1-7	as originally filed
Claims, Numbers	
1-28	as originally filed
Claims, Pages	
18-21	as originally filed
Drawings, Sheets	
1-5	as originally filed
Drawings, Figures	
1-5	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-12, 21-26, and 28 partially

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-12, 21-26, and 28 partially

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/004132

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	13-17, 20, 26-28
	No:	Claims	1-12, 18-19, 21-25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

According to Rule 66.1(e) PCT, claims relating to inventions in respect of which no international search report has been established need not to be the subject of an international preliminary examination. Therefore, the present opinion is limited to the subject-matter that has been searched, namely claims 13-20, 27, and claims 1-12, 21-26, 28 partially.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. From the application as filed, it is clear that the wording "GPR54 receptor" corresponds to at least two different amino acid sequences (SEQ ID N°2 and SEQ ID N°3). However, the protein of SEQ ID N°3 was not disclosed in the priority document. Therefore, the date of priority claimed (02.04.03) cannot be allowed for claims 1-28 as far as they related to SEQ ID N°3 or fragment thereof (Articles 54(2) and 89 EPC).

2. Reference is made to the following documents:

D1: EP A 1126028
D2: WO 03/003983
D3: de Roux N. et al., Hypogonadotropic hypogonadism due to loss of function of the kiss-derived peptide receptor GPR54. PNAS. 2003. 100: 10972-10976.

Novelty (Article 33(2) PCT)

The subject-matter of claims 1-12, 18-19, and 21-25 is not novel.

The subject-matter of claims 1-12 and 21-25 is not novel since D1 disclosed Kiss-1 peptides (in particular peptide 45-54) and medical applications of them. Document D2 discloses also Kiss-1 peptides and their uses in medicine. Therefore, product claims and first medical use claims, i.e claims 1-12 and 21-25 are anticipated by D1 and D2.

The fragment of the GPR54 of SEQ ID N°2 carrying the mutation L102P and the fragment from amino acids 247 to 398 do not form part of the prior art known from the examining division but the same subject-matter related to SEQ ID N°3 (for which the priority cannot be recognized) is known from D3.
Therefore, novelty is not acknowledged for claims 18-19 as far as they are related to SEQ ID N°3.

However, methods for screening a compound that affects the gonadotropic axis comprising the step of assaying the compound in the presence of a GRP54 receptor do not form part of the prior art known to the examining division. Novelty can therefore be acknowledged for claims 13-17.

Finally, no composition comprising kiss-1 or kiss-1 peptides and GnRH was described in the prior art. Therefore, novelty can be recognized for the subject-matter of claims 26-28.

Inventive step (Article 33(3) PCT)

For claims for which priority was considered to be valid (claims 1-28 related to SEQ ID N°2):

Since nothing in the prior art suggests that the receptor GPR54 is implicated in the gonadotropic axis regulation, the method of claim 13 is considered to be inventive. Therefore, inventivity can also be acknowledged for the claims depending thereon, i.e. claims 14-17.

The phenotype associated with the mutation L102P was not foreseeable from the prior art. Therefore, inventivity can be recognized for the subject-matter of claims 19 and 20 when referring to the antibody specific to the protein of claim 19.

However, the fragment 247-398 of the SEQ ID N°2 cannot be considered as inventive, since no technical feature was shown to be associated with this fragment. Moreover, in the absence of determining a function for the fragment it is not possible to see what kind of problem should be solved by this fragment or if there is a problem or whether it has actually been solved. Therefore, inventivity has to be denied for claims 18 and 20 when referring to the antibody specific to the protein of claim 18.

Finally, the subject-matter of claims 26-28 seems to be inventive since the effect due to the combination of GnRH and Kiss-1 (45-54) peptide on the secretion of LH and FSH was not foreseeable from the prior art.

For claims for which priority was considered to be not valid (claims 1-28 related to SEQ ID N°3):

They are obvious in view of D3.

Further remarks:

The antibodies claimed in claim 20 cannot be specific to the proteins of claim 18, as the fragment 247 to 398 is present in the full length proteins of SEQ ID N°2 and 3.